

(FILE 'HOME' ENTERED AT 15:29:11 ON 21 DEC 1999)

FILE 'EMBASE, MEDLINE, BIOSIS, CAPLUS, SCISEARCH, TOXLINE, CANCERLIT,
APIPAT, CROPU, DGENE, DPCI, EUROPATFULL, IFIPAT, INPADOC, JAPIO,
PAPERCHEM2, PATDD, PATDPA, PATOSDE, PATOSEP, PATOSWO, PIRA, RAPRA,
TULSA,
TULSA2, USPATFULL' ENTERED AT 15:30:20 ON 21 DEC 1999
L1 615 S (BAG(3A) (GENE OR PROTEIN#))
L2 88 S L1 (30A) (CANCER OR CARCINOMA OR TUMOUR OR TUMOR OR MALIGNAN
L3 32 DUP REM L2 (56 DUPLICATES REMOVED)

L3 ANSWER 11 OF 32 SCISEARCH COPYRIGHT 1999 ISI (R)
 AN 1999:493789 SCISEARCH
 GA The Genuine Article (R) Number: 196PK
 TI Expression patterns and subcellular distribution of the anti-apoptotic
protein Bag-1 in normal and **malignant** oral
 epithelium: relation to cellular differentiation and prognosis for oral
 squamous cell **carcinoma**.
 AU Hague A (Reprint); Packham G; Huntley S; Heung Y L
 CS UNIV BRISTOL, DEPT ORAL & DENT SCI, BRISTOL, AVON, ENGLAND; IMPERIAL COLL
 ST MARYS, LUDWIG INST CANC RES, LONDON W2 1PG, ENGLAND
 CYA ENGLAND
 SO JOURNAL OF DENTAL RESEARCH, (MAY 1999) Vol. 78, No. 5, pp. 1082-1082.
 Publisher: AMER ASSOC DENTAL RESEARCH, 1619 DUKE ST, ALEXANDRIA, VA
 22314.
 ISSN: 0022-0345.
 DT Conference; Journal
 FS LIFE; CLIN
 LA English
 REC Reference Count: 0
 TI Expression patterns and subcellular distribution of the anti-apoptotic
protein Bag-1 in normal and **malignant** oral
 epithelium: relation to cellular differentiation and prognosis for oral
 squamous cell **carcinoma**.

L3 ANSWER 12 OF 32 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.DUPLICATE 4
 AN 1999293002 EMBASE
 TI Overexpression of anti-apoptotic **gene BAG-1** in human
 cervical **cancer**.
 AU Yang X.; Hao Y.; Ferenczy A.; Tang S.-C.; Pater A.
 CS A. Pater, Division of Basic Medical Sciences, Faculty of Medicine,
 Memorial University of Newfoundland, St. John's, Nfld. A1B 3V6, Canada.
 apater@morgan.ucs.mun.ca
 SO Experimental Cell Research, (25 Feb 1999) 247/1 (200-207).
 Refs: 52
 ISSN: 0014-4827 CODEN: ECREAL
 CY United States
 DT Journal; Article
 FS 010 Obstetrics and Gynecology
 016 Cancer
 022 Human Genetics
 LA English
 SL English
 AB Apoptosis is a programmed cell death process in which cells commit
 suicide
 under certain environmental conditions. Recent studies suggest that
 apoptosis is controlled by a variety of cellular genes, and dysregulation
 of these genes plays an important role in the pathogenesis of human
 diseases, including cancer. BAG-1 is a novel anti-apoptotic protein
 isolated by its interaction with another anti-apoptotic protein, Bcl-2.
 It
 binds to several hormone receptors and growth factor receptors and
 modulates their function in apoptosis. However, the role of BAG-1 in the
 oncogenesis of human cervical cancer has yet to be illustrated. In this
 study, we examined the expression of BAG-1 in cervical normal and
 carcinoma cultured cells and tissues. BAG-1 was overexpressed in human
 cervical carcinoma cell lines and tissues. Overexpression was regulated
 at
 the transcriptional level. The increased expression of BAG-1 was
 correlated with enhanced resistance of cervical carcinoma cells to

apoptosis induced by a DNA-damaging reagent. In addition, overexpression of BAG-1 enhanced the resistance of cervical cells to apoptosis. This study provided the first evidence that BAG-1 is upregulated in human cervical cancer and may play an important role in apoptosis and human cervical carcinogenesis.

TI Overexpression of anti-apoptotic **gene BAG-1** in human cervical **cancer**.

L3 ANSWER 13 OF 32 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.DUPLICATE 5
AN 1999150399 EMBASE

TI Prognostic significance of apoptosis regulators in breast cancer.

AU Krajewski S.; Krajewska M.; Turner B.C.; Pratt C.; Howard B.; Zapata J.M.;

Frenkel V.; Robertson S.; Ionov Y.; Yamamoto H.; Perucho M.; Takayama S.; Reed J.C.

CS S. Krajewski, Burnham Institute, Program on Apoptosis/Cell Death Res., 10901 North Torrey Pines Road, San Diego, CA 92037, United States

SO Endocrine-Related Cancer, (1999) 6/1 (29-40).

Refs: 78

ISSN: 1351-0088 CODEN: ERCAE

CY United Kingdom

DT Journal; General Review

FS 003 Endocrinology

005 General Pathology and Pathological Anatomy

016 Cancer

LA English

SL English

AB Dysregulation of normal programmed cell death mechanisms plays an important role in the pathogenesis and progression of breast cancer, as well as in responses of tumors to therapeutic intervention.

Overexpression

of anti-apoptotic members of the Bcl-2 family such as Bcl-2 and Bcl-x(L) has been implicated in cancer chemoresistance, whereas high levels of

pro-

apoptotic proteins such as Bax promote apoptosis and sensitize tumor

cells

to various anticancer therapies. Though the mechanisms by which Bcl-2 family proteins regulate apoptosis are diverse, ultimately they govern decision steps that determine whether certain caspase family cell death proteases remain quiescent or become active. To date, approximately 17 cellular homologs of Bcl-2 and at least 15 caspases have been identified in mammals. Other types of proteins may also modulate apoptotic responses through effects on apoptosis-regulatory proteins, such as BAG-1 - a heat shock protein 70 kDa (Hsp70/Hsc70)-binding protein that can modulate stress responses and alter the functions of a variety of proteins

involved

in cell death and division. In this report, we summarize our attempts

thus

far to explore the expression of several Bcl-2 family **proteins**,

caspase-3, and **BAG-1** in primary breast **cancer**

specimens and breast **cancer** cell lines. Moreover, we describe

some of our preliminary observations concerning the prognostic

significance of these apoptosis regulatory proteins in breast

cancer patients, contrasting results derived from women with

localized disease (with or without node involvement) and metastatic cancer.

AB . . . death and division. In this report, we summarize our attempts

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prognostic

significance of these apoptosis regulatory proteins in breast

cancer patients, contrasting results derived from women with

localized disease (with or without node involvement) and metastatic

L3 ANSWER 15 OF 32 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.DUPLICATE 6
 AN 1998227564 EMBASE
 TI Interaction of BAG-1 with retinoic acid receptor and its inhibition of
 retinoic acid-induced apoptosis in cancer cells.
 AU Liu R.; Takayama S.; Zheng Y.; Froesch B.; Chen G.-Q.; Zhang X.; Reed
 J.C.; Zhang X.-K.
 CS X.-K. Zhang, Burnham Institute, Cancer Research Center, 10901 N. Torrey
 Pines Rd., San Diego, CA 92037, United States. xzhang@ljcrf.edu
 SO Journal of Biological Chemistry, (3 Jul 1998) 273/27 (16985-16992).
 Refs: 52
 ISSN: 0021-9258 CODEN: JBCHA3
 CY United States
 DT Journal; Article
 FS 016 Cancer
 029 Clinical Biochemistry
 LA English
 SL English
 AB BAG-1 (also known as HAP46) is an anti-apoptotic protein, which has been
 shown previously to interact with a number of nuclear hormone receptors,
 including receptors for glucocorticoid, estrogen, and thyroid hormone. We
 show here that BAG-1 also interacts with retinoic acid receptor (RAR).
 Gel retardation assays demonstrated that in vitro translated BAG-1 protein
 could effectively inhibit the binding of RAR but not retinoid X receptor
 (RXR) to a number of retinoic acid (RA) response elements (RAREs). A
 glutathione S- transferase-BAG-1 fusion protein also specifically bound
 RAR but not RXR. Interaction of BAG-1 and RAR could also be demonstrated
 by yeast two-hybrid assays. In transient transfection assays,
 co-transfection of BAG-1 expression plasmid inhibited the transactivation
 activity of RAR/heterodimers but not RXR/RXR homodimers. When stably
 expressed in breast cancer cell lines, BAG-1 inhibited binding of RAR/RXR
 heterodimer to a number of RAREs and suppressed RA-induced growth
 inhibition and apoptosis. In addition, RA-induced suppression of Bcl-2
 expression was abrogated by overexpression of BAG-1. These results
 demonstrate that BAG-1 can regulate retinoid activities through its
 interaction with RAR and suggest that elevated levels of **BAG-1**
protein could potentially contribute to retinoid resistance in
cancer cells.
 AB . . . These results demonstrate that BAG-1 can regulate retinoid
 activities through its interaction with RAR and suggest that elevated
 levels of **BAG-1 protein** could potentially contribute
 to retinoid resistance in **cancer** cells.

L3 ANSWER 16 OF 32 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.DUPLICATE 7
 AN 1998197198 EMBASE
 TI BAG-1L protein enhances androgen receptor function.
 AU Froesch B.A.; Takayama S.; Reed J.C.
 CS J.C. Reed, Burnham Institute, 10901 N. Torrey Pines Rd., San Diego, CA
 92037, United States. jreed@burnham-inst.org
 SO Journal of Biological Chemistry, (8 May 1998) 273/19 (11660-11666).
 Refs: 41
 ISSN: 0021-9258 CODEN: JBCHA3
 CY United States
 DT Journal; Article
 FS 016 Cancer
 029 Clinical Biochemistry
 LA English
 SL English
 AB BAG-1 is a regulator of heat shock protein (Hsp) 70/Hsc70 family proteins

that interacts with steroid hormone receptors. The recently identified BAG-1 long (**BAG-1L**) **protein**, an isoform of **BAG-1** that arises from translation initiation at a noncanonical CUG codon, was co-immunoprecipitated with androgen receptors (AR) from LNCaP prostate **cancer** cells and other cell lysates, whereas the shorter originally identified BAG-1 and **BAG-1M** (RAP 46) **proteins** were not. **BAG-1L**, but not BAG-1 or BAG-1M (RAP46), also markedly enhanced the ability of AR to transactivate reporter gene plasmids containing an androgen response element (ARE) in PC3 prostate **cancer** and other cell lines. A C-terminal region deletion mutant of BAG-1L failed to co-immunoprecipitate with AR and functioned as a trans-dominant inhibitor of BAG-1L, impairing AR-induced transactivation of ARE-containing reporter plasmids. In addition, BAG-1L significantly reduced the concentrations of 5.alpha.-dihydrotestosterone (DHT) required for AR activity but did not induce ligand-independent transactivation. BAG-1L also markedly improved the ability of AR to transactivate reporter genes when cells were cultured with DHT in combination with the anti-androgen cyproterone acetate. The effects of BAG-1L on AR could not be explained by detectable alterations in the DHT-induced translocation of AR from cytosol to nucleus, nor by BAG-1L-induced increases in the amounts of AR **protein**. These findings implicate **BAG-1L** in the regulation of AR function and may have relevance to mechanisms of prostate **cancer** resistance to hormone-ablative and anti-androgen therapy.

AB . . . regulator of heat shock protein (Hsp) 70/Hsc70 family proteins that interacts with steroid hormone receptors. The recently identified BAG-1 long (**BAG-1L**) **protein**, an isoform of **BAG-1** that arises from translation initiation at a noncanonical CUG codon, was co-immunoprecipitated with androgen receptors (AR) from LNCaP prostate **cancer** cells and other cell lysates, whereas the shorter originally identified BAG-1 and **BAG-1M** (RAP 46) **proteins** were not. **BAG-1L**, but not BAG-1 or BAG-1M (RAP46), also markedly enhanced the ability of AR to transactivate reporter gene plasmids containing an androgen response element (ARE) in PC3 prostate **cancer** and other cell lines. A C-terminal region deletion mutant of BAG-1L failed to co-immunoprecipitate with AR and functioned as . . . alterations in the DHT-induced translocation of AR from cytosol to nucleus, nor by BAG-1L-induced increases in the amounts of AR **protein**. These findings implicate **BAG-1L** in the regulation of AR function and may have relevance to mechanisms of prostate **cancer** resistance to hormone-ablative and anti-androgen therapy.

L3 ANSWER 17 OF 32 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.DUPLICATE 8
AN 1998243196 EMBASE
TI Expression and location of Hsp70/Hsc-binding anti-apoptotic **protein BAG-1** and its variants in normal tissues and **tumor** cell lines.
AU Takayama S.; Krajewski S.; Krajewska M.; Kitada S.; Zapata J.M.; Kristine Z.; Kochel K.; Knee D.; Scudiero D.; Tudor G.; Miller G.J.; Miyashita T.; Yamada M.; Reed J.C.
CS J.C. Reed, Burnham Institute, 10901 North Torrey Pines Road, San Diego, CA 92037, United States. jreed@burnham-inst.org
SO Cancer Research, (15 Jul 1998) 58/14 (3116-3131).
Refs: 32
ISSN: 0008-5472 CODEN: CNREA8
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
016 Cancer

LA English
SL English
AB BAG-1 is a multifunctional protein that blocks apoptosis and interacts with several types of proteins, including Bcl-2 family proteins, the kinase Raf-1, certain tyrosine kinase growth factor receptors, and steroid hormone receptors, possibly by virtue of its ability to regulate the Hsp70/Hsc70 family of molecular chaperones. Two major forms of the human and mouse BAG-1 proteins were detected by immunoblotting. The longer and mouse BAG-1 proteins (BAG-1L) appear to arise through translation initiation at noncanonical CTG codons located upstream of and in-frame with the usual ATG codon used for production of the originally described BAG-1 protein. Immunoblotting experiments using normal tissues revealed that BAG-1L is far more restricted in its expression and is present at lower levels than the more prevalent BAG-1 protein. Human but not mouse tissues also produce small amounts of an additional isoform of BAG-1 of intermediate size (BAG-1M) that probably arises through translation initiation at yet another site involving an ATG codon. All three isoforms of human BAG-1 (BAG-1, BAG-1M, and BAG-1L) retained the ability to bind Hsc70. Subcellular fractionation and immunofluorescence confocal microscopy studies indicated that BAG-1L often resides in the nucleus, consistent with the presence of a nuclear localization sequence in the NH2-terminal unique domain of this protein. In immunohistochemical assays, BAG-1 immunoreactivity was detected in a wide variety of types of cells in normal adult tissues and was localized to either cytosol, nucleus, or both, depending on the particular type of cell. In some cases, cytosolic BAG-1 immunostaining was clearly associated with organelles resembling mitochondria, consistent with the reported interaction of BAG-1 with Bcl-2 and related proteins. Furthermore, experiments using a green fluorescence protein (GFP)-BAG-1 fusion protein demonstrated that overexpression of Bcl-2 in cultured cells can cause intracellular redistribution of GFP-BAG-1, producing a membranous pattern typical of Bcl-2 family proteins. The BAG-1 protein was found at high levels in several types of human tumor cell lines among the 67 tested, particularly leukemias, breast, prostate, and colon cancers. In contrast to normal tissues, which only rarely expressed BAG-1L, tumor cell lines commonly contained BAG-1L protein, including most prostate, breast, and leukemia cell lines, suggesting that a change in BAG-1 mRNA translation frequently accompanies malignant transformation.

TI Expression and location of Hsp70/Hsc-binding anti-apoptotic protein BAG-1 and its variants in normal tissues and tumor cell lines.

AB . . . overexpression of Bcl-2 in cultured cells can cause intracellular redistribution of GFP-BAG-1, producing a membranous pattern typical of Bcl-2 family proteins. The BAG-1 protein was found at high levels in several types of human tumor cell lines among the 67 tested, particularly leukemias, breast, prostate, and colon cancers. In contrast to normal tissues, which only rarely expressed BAG-1L, tumor cell lines commonly contained BAG-1L protein, including most prostate, breast, and leukemia cell lines, suggesting that a change in BAG-1 mRNA translation frequently accompanies malignant transformation.

L3 ANSWER 18 OF 32 BIOSIS COPYRIGHT 1999 BIOSIS DUPLICATE 9
AN 1998:305490 BIOSIS
DN PREV199800305490
TI Prolonged cell survival enhances peritoneal dissemination of gastric cancer cells.
AU Yawata, Atsushi; Adachi, Masaaki (1); Okuda, Hiroyuki; Naishiro, Yasuyoshi; Takamura, Takenori; Hareyama, Masato; Takayama, Shinichi;
Reed,

John C.; Imai, Koh-ichi
CS (1) First Dep. Intern. Med., Sapporo Med. Univ. Sch. Med., Sapporo 060
Japan
SO Oncogene, (May 21, 1998) Vol. 16, No. 20, pp. 2681-2686.
ISSN: 0950-9232.
DT Article
LA English
AB Bcl-2 and a Bcl-2-binding protein BAG-1 function in protection from
apoptosis induced by a variety of stimuli. Deregulated expression of
Bcl-2

leads to inhibition of apoptosis and is correlated with development of various cancers. Here, we provide evidence that prolonged cell survival introduced by overproduction of Bcl-2 or BAG-1 strongly enhances peritoneal dissemination of human gastric cancer MKN74 cells. Gene transfer-mediated overexpression of Bcl-2 or BAG-1 led to prolonged cell survival of MKN74 cells against serum-starved apoptosis and anoikis. When the viable transfectants were inoculated into the intraperitoneal cavity of BALB/c nude mice, the Bcl-2-expressing MKN74 cells and the BAG-1-expressing MKN74 cells exhibited strongly enhanced peritoneal dissemination in BALB/c nude mice and whole disseminated tumor weights were increased by 4-fold and 3.3-fold, respectively, compared with the control transfectants. The enhanced peritoneal dissemination of MKN74-Bcl-2 and MKN74-BAG-1 transfectants correlated well with resistance to cell death induced by serum-starvation and anoikis. However, the overexpression of Bcl-2 or BAG-1 caused no significant difference among the transfectants in cell growth rates, either in vitro or in vivo. Taken together, these studies demonstrate that resistance to apoptosis is a crucial factor for development of peritoneal dissemination of human gastric cancer cells.

IT Major Concepts
Tumor Biology
IT Chemicals & Biochemicals

L3 ANSWER 20 OF 32 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.DUPLICATE 11
 AN 1998312706 EMBASE
 TI Human **BAG-1/RAP46 protein** is generated as four
 isoforms by alternative translation initiation and overexpressed in
cancer cells.
 AU Yang X.; Chernenko G.; Hao Y.; Ding Z.; Pater M.M.; Pater A.; Tang S.-C.
 CS S.-C. Tang, Basic Medical Sciences, Faculty of Medicine, Memorial
 University of Newfoundland, 300 Prince Philip Drive, St John's, Nfld. A1B
 3V6, Canada
 SO Oncogene, (27 Aug 1998) 17/8 (981-989).
 Refs: 27
 ISSN: 0950-9232 CODEN: ONCNES
 CY United Kingdom
 DT Journal; Article
 FS 016 Cancer
 022 Human Genetics
 LA English
 SL English
 AB Previously, a Bcl-2-interacting protein, BAG-1, was cloned from mouse
 cells and was shown to interact with several other proteins and to be
 important for inhibition of apoptosis. Human BAG-1 (hBAG-1) cDNA,
 recently
 isolated by us and two other groups, has been shown to be identical to a
 hormone receptor-binding protein, RAP46. However, different molecular
 masses of hBAG-1 protein products were noted by these three groups. Here
 we demonstrated that hBAG-1 protein was expressed as four isoforms,
 designated p50, p46, p33 and p29, with apparent molecular masses of 50
 kDa, 46 kDa, 33 kDa and 29 kDa, respectively. Deletion, site-directed
 mutagenesis and in vitro transcription/translation analysis showed that
 the four protein products of hBAG-1 were expressed by alternative
 initiation from four different start codons through a leaky scanning
 mechanism. Furthermore, we demonstrated that the distinct forms of hBAG-1
 have different subcellular localizations, suggesting that they may have
 distinct functions in the cells. Characterization of hBAG-1 RNA and
 protein also showed that hBAG-1 was overexpressed in human cervical,
 breast and lung cancer cell lines. Taken together, these data clarify the
 conflicting observations reported in the literature and suggest that
 hBAG-1 is expressed as four forms of protein products, which may play a
 differential role in apoptosis and oncogenesis of human cells.
 TI Human **BAG-1/RAP46 protein** is generated as four
 isoforms by alternative translation initiation and overexpressed in
cancer cells.

L3 ANSWER 21 OF 32 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
 AN 1998084196 EMBASE
 TI Molecular targeting therapy for cancer.
 AU Hinoda Y.; Naeshiro Y.; Imai K.
 CS Dr. Y. Hinoda, First Dept. of Internal Medicine, Sapporo Medical
 University, Minami-1-jo Nishi-16-chome, Chuo-ku, Sapporo 060-0061, Japan
 SO Biotherapy, (1998) 12/2 (290-296).
 Refs: 20
 ISSN: 0914-2223 CODEN: BITPE
 CY Japan
 DT Journal; Article
 FS 016 Cancer
 022 Human Genetics
 026 Immunology, Serology and Transplantation
 LA Japanese
 SL English; Japanese

AB The mechanisms of carcinogenesis and cancer development have recently
been clarified at the molecular level. It is now possible to develop a cancer
therapy to regulate the expression of a molecule as a therapeutic target.
MUC1 mucin is considered to be an important therapeutic target molecule
from two viewpoints. One is the inducibility of HLA-unrestricted and
MUC1-specific cytotoxic T lymphocytes in various cancer patients. Their
ex vivo expansion against autologous MUC1 cDNA transfected B-cells is
expected to be applicable for cancer therapy. The other is a possible
role of MUC1 mucin in cancer invasion. Recent immunohistochemical findings
have suggested that MUC1 is predominantly expressed in a type of invasive
cancer. Both in vitro and in vivo invasiveness of gastric cancer MKN74
cells was increased by MUC1 cDNA transfection. KAI1 was cloned as a
metastasis suppressor gene for prostate cancer. Recent evidences have
suggested that KAI1 may behave as a metastasis suppressor in various
cancers other than prostate **cancer**. Decreased motility and
invasiveness of colon **cancer** cells resulted in KAI1 cDNA
transfection. Bcl-2 is known to inhibit apoptosis from a variety of
stimuli. A Bcl-2- binding **protein BAG-1** also functions
to protect against apoptosis in concert with Bcl-2. We provided evidences
that prolonged cell survival introduced by overexpression of Bcl-2 or
BAG-1 proteins strongly promotes experimental pulmonary
metastasis of melanoma cells. The development of more effective
regulators for those gene expressions and of vectors with targeting
function will facilitate clinical application of molecular targeting
therapy for cancer.

AB . . . prostate cancer. Recent evidences have suggested that KAI1 may
behave as a metastasis suppressor in various cancers other than prostate
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proteins strongly promotes experimental pulmonary
metastasis of melanoma cells. The development of more effective
regulators for those gene expressions and of vectors with targeting
function will. . .

L3 ANSWER 22 OF 32 CAPLUS COPYRIGHT 1999 ACS

AN 1998:136934 CAPLUS

DN 128:255783

TI Expression of multiple apoptosis-regulatory genes in human breast cancer
cell lines and primary tumors

AU Zapata, Juan M.; Krajewska, Maryla; Krajewski, Stanislaw; Huang, Ruo-Pan;
Takayama, Shinichi; Wang, Hong-Gang; Adamson, Eileen; Reed, John C.

CS Cancer Research Center, Oncogene & Tumor Suppressor Gene Program, The
Burnham Inst., La Jolla, CA, 92037, USA

SO Breast Cancer Res. Treat. (1998), 47(2), 129-140

CODEN: BCTRD6; ISSN: 0167-6806

PB Kluwer Academic Publishers

DT Journal

LA English

AB The expression of several apoptosis-regulating genes was evaluated in 9
human breast cancer cell lines, 2 immortalized human mammary epithelial
lines, 1 normal breast tissue biopsy, and 3 primary breast tumors, using

a multiple antigen detection (MAD) immunoblotting method. The
anti-apoptotic proteins Bcl-2, Bcl-XL Mcl-1, and BAG-1 were present at
immunodetectable levels in 7, 10, 10, and 9 of the 11 lines. Comparing
these 11 cell lines among themselves revealed that steady-state levels of
Bcl-2, Bcl-XL Mcl-1, and BAG-1 were present at relatively higher levels
in

4, 6, 5, and 5 of the lines, resp. In contrast, the pro-apoptotic proteins Bax and Bak were detected in all 11 cell lines, and were present at relatively higher levels in 10 and 5 of the 11 lines, resp. The Interleukin-1.β converting enzyme (ICE) homolog CPP32 (Caspase-3) was expressed in 10/11 breast cell lines. High levels of p53 protein, indicative of mutant p53, were found in 8 of the 11 lines and correlated inversely with Bax expression. Bcl-2 and BAG-1 protein levels were positively correlated. Immunoblot anal. of primary adenocarcinomas revealed expression of the anti-apoptotic proteins Bcl-2, Bcl-XL, Mcl-1, and BAG-1, as well as the pro-apoptotic proteins Bax, Bak, and CPP32, in at least 2 of the 3 tumors examined. Immunohistochem. anal. was also performed for all of these proteins using 20 paraffin-embedded breast cancer biopsy specimens that all contained residual normal mammary epithelium in combination with both invasive cancer and carcinoma in situ. All of

these

apoptosis-regulating proteins were detected in primary breast cancers, though the percentage of immunopos. tumor cells varied widely in some cases. Comparisons of the intensity of immunostaining in normal mammary epithelium and invasive carcinoma suggested that Bcl-2 immunointensity tends to be lower in cancers than normal breast epithelium, whereas CPP32 immunointensity was generally higher in invasive cancers. The results demonstrate expression of multiple apoptosis-modulating proteins in

breast

cancer cell lines and primary tumors, suggesting complexity in the regulation of apoptosis in these neoplasms of mammary epithelial origin.

IT Proteins (specific **proteins** and subclasses)

RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)

(**gene BAG-1**; expression of multiple apoptosis-regulatory genes in human breast **cancer** cell lines and primary tumors)

L3 ANSWER 23 OF 32 BIOSIS COPYRIGHT 1999 BIOSIS

AN 1998:364793 BIOSIS

DN PREV199800364793

TI Enhanced expression of anti-apoptotic proteins in human papillomavirus-immortalized and cigarette smoke condensate-transformed human endocervical cells: Correlation with resistance to apoptosis

induced

by DNA damage.

AU Yang, Xiaolong; Hao, Yawei; Pater, Mary M.; Tang, Shou-Ching; Pater, Alan (1)

CS (1) Div. Basic Med. Sci., Fac. Med., Memorial Univ. Newfoundland, St. John's, Newfoundland A1B 3V6 Canada

SO Molecular Carcinogenesis, (June, 1998) Vol. 22, No. 2, pp. 95-101. ISSN: 0899-1987.

DT Article

LA English

AB Apoptosis plays an important role in various biological processes including embryogenesis, differentiation, homeostasis, and oncogenesis.

We

have developed a system composed of primary human endocervical cells (HEN), HEN immortalized by human papillomavirus (HPV) type 16, and their counterparts subsequently malignantly transformed by cigarette smoke condensate (CSC). To understand the role of apoptosis in the multistep oncogenesis of human cervical cells, we examined the expression of apoptosis-associated proteins in our in vitro model system. The results showed no significant difference in the levels of apoptosis-inducing proteins bak and bax among all the cell types examined. On the other

hand,

the levels of apoptosis-inhibiting proteins bcl-2, bcl-xL and BAG-1 increased progressively after immortalization and transformation. The p53 protein level decreased in the HPV16-immortalized HEN and increased in

one

of two lines of the CSC-transformed HEN. Further, the increased levels of apoptosis-inhibiting proteins in the HPV16-immortalized and the

CSC-transformed H₁₂ correlated with progressively increased resistance of these cells to apoptosis induced by staurosporine or cisplatin. This study

provided the first evidence that overexpression of apoptosis-inhibiting proteins is important for both multistep oncogenesis and resistance of human endocervical cells to apoptosis induced by DNA-damaging reagents.

IT . . .
damage-induced apoptosis resistance correlation, enhanced tumor cell expression; bcl-2 anti-apoptotic protein: DNA damage-induced apoptosis resistance correlation, enhanced tumor cell expression; **BAG-1** anti-apoptotic **protein**: DNA damage-induced apoptosis resistance correlation, enhanced **tumor** cell expression

L3 ANSWER 27 OF 32 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.DUPLICATE 12
AN 97225294 EMBASE
DN 1997225294

TI Anti-cell death activity promotes pulmonary metastasis of melanoma cells.

AU Takaoka A.; Adachi M.; Okuda H.; Sato S.; Yawata A.; Hinoda Y.; Takayama S.; Reed J.C.; Imai K.

CS M. Adachi, First Department Internal Medicine, Sapporo Medical University,

School of Medicine, Sapporo 060, Japan

SO Oncogene, (1997) 14/24 (2971-2977).

Refs: 29

ISSN: 0950-9232 CODEN: ONCNES

CY United Kingdom

DT Journal; Article

FS 016 Cancer

022 Human Genetics

LA English

SL English

AB Bcl-2 inhibits apoptosis from a variety of stimuli, and a Bcl-2-binding protein BAG-1 also functions in protection from apoptosis in concert with Bcl-2. Here, we provide evidence that prolonged cell survival introduced by overexpression of Bcl-2 or **BAG-1 proteins** strongly promotes experimental pulmonary **metastasis** of melanoma B16-BL6 cells. In murine melanoma cell line B16-BL6, gene transfer-mediated expression of the Bcl-2 or BAG-1 led to prolonged cell survival against serum-starved apoptosis in vitro. The Bcl-2-expressing B16 cells, B16-Bcl-2 and the BAG-1-expressing B16 cells, B16-BAG-1 strongly enhanced pulmonary metastasis in allogenic BALB/c nude mice and whole lung weights were increased by 2.4-fold and 1.4-fold, respectively, compared with control transfectants, suggesting that Bcl-2 is a stronger positive modulator of metastasis. When the viable B16-Bcl-2 and control transfectants were injected subcutaneously into BALB/c nude mice, the colony numbers of pulmonary metastasis of the B16-Bcl-2 transfectant increased by 5.6-fold compared with the control transfectants. These enhanced metastatic potentials in the B16-Bcl-2 and the B16-BAG-1 transfectants were well correlated with anti-cell death activity against serum-starvation and enhanced cell viability on limiting dilution. Analysis of the transfectants however revealed that their growth rates, invasive ability and cell motility were not significantly altered by overexpression of either Bcl-2 or **BAG-1 proteins**. Taken together, these studies demonstrate that prolonged cell survival is a crucial factor to promote **metastasis** of melanoma, thereby contributing to **tumor** progression.

AB . . . from apoptosis in concert with Bcl-2. Here, we provide evidence that prolonged cell survival introduced by overexpression of Bcl-2 or **BAG-1 proteins** strongly promotes experimental pulmonary **metastasis** of melanoma B16-BL6 cells. In murine melanoma cell line B16-BL6, gene transfer-mediated expression of the Bcl-2 or BAG-1 led to. . . revealed that their growth rates, invasive ability and cell motility

were not significantly altered by overexpression of either Bcl-2 or **BAG-1 proteins**. Taken together, these studies demonstrate that prolonged cell survival is a crucial factor to promote **metastasis** of melanoma, thereby contributing to **tumor** progression.

L3 ANSWER 28 OF 32 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1998:107896 BIOSIS

DN PREV199800107896
 TI Inhibition of apoptosis with Bcl-2 or BAG-1 promotes peritoneal dissemination of human gastric cancer cells.
 AU Yawata, A.; Adachi, M.; Okuda, H.; Itoh, F.; Kato, Y.; Hinoda, Y.; Yachi, A.; Imai, K.
 CS First Dep. Internal Med., Sapporo Med. Univ. Sch. Med., Sapporo 060 Japan
 SO Tumor Biology, (Sept., 1997) Vol. 18, No. SUPPL. 2, pp. 124.
 Meeting Info.: Meeting on From Basic Cancer Research to Clinical Application held at the XXVth Anniversary Meeting of the International Society for Oncodevelopmental Biology and Medicine Montreux, Switzerland September 19-24, 1997 International Society for Oncodevelopmental Biology and Medicine
 . ISSN: 1010-4283.
 DT Conference
 LA English
 IT
 IT and Molecular Biophysics); Tumor Biology
 IT Chemicals & Biochemicals
 Bcl-2 protein gene: apoptosis inhibitor, tumor cell expression, peritoneal dissemination promoter; **BAG-1 protein gene: apoptosis inhibitor, tumor cell expression, peritoneal dissemination promoter**

L3 ANSWER 29 OF 32 BIOSIS COPYRIGHT 1999 BIOSIS
 AN 1998:69792 BIOSIS
 DN PREV199800069792
 TI Characterization of the subcellular location of **BAG-1 protein** in human breast **cancer**.
 AU Turner, B. C. (1); Krajewska, M.; Krajewski, S.; Wang, L. (1); Carter, D.; Takayama, S.; Kochel, K.; Glazer, P. M.; Haffty, B. G. (1); Reed, J. R. (1) Dep. Therapeutic Radiol., Yale Univ. Sch. Med., New Haven, CT USA
 CS Breast Cancer Research and Treatment, (Oct., 1997) Vol. 46, No. 1, pp. 69.
 Meeting Info.: 20th Annual San Antonio Breast Cancer Symposium San Antonio, Texas, USA December 3-6, 1997
 ISSN: 0167-6806.
 DT Conference
 LA English
 TI Characterization of the subcellular location of **BAG-1 protein** in human breast **cancer**.

L3 ANSWER 30 OF 32 CAPLUS COPYRIGHT 1999 ACS
 AN 1997:124475 CAPLUS
 DN 126:126901
 TI Apoptin in induction of p53-independent apoptosis in transformed cells, use in tumor therapy, apoptin localization, and diagnostic test for cell-transforming activity
 IN Noteborn, Matheus Hubertus Mari
 PA Aesculaap B.V., Neth.
 SO PCT Int. Appl., 39 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 FAN.CNT 5

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9641191	A1	19961219	WO 1996-NL229	19960607
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
	CA 2221495	AA	19961219	CA 1996-2221495	19960607
	AU 9659136	A1	19961230	AU 1996-59136	19960607

EP 830604 19980325 EP 1996-9161 19960607
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, FI
JP 11506340 T2 19990608 JP 1996-500327 19960607
US 5958424 A 19990928 US 1997-910618 19970813
PRAI US 1995-484939 19950607
NL 1990-2008 19900912
WO 1996-N
L229 19960607
AB The invention describes that apoptin fails to induce apoptosis in human
normal cells, and that when normal cells are transformed, they become
susceptible to the apoptin-induced apoptosis. Apoptin induces in various
human tumor cells a p53-distinct type of apoptosis, and cannot be blocked
by a variety of apoptosis-inhibiting agents. The invention comprises an
anti-tumor agent which specifically kills tumor cells and not normal
cells. It further provides the induction of cell death by means of gene
therapy. Apoptin can induce apoptosis in non-human animal tumor cells.
In normal cells apoptin was found predominantly in the cytoplasm, while
in
tumor cells it was located in the nucleus. The invention further
comprises a diagnostic test for the detn. of cell-transforming activity.
IT Proteins (specific **proteins** and subclasses)
RL: BAC (Biological activity or effector, except adverse); BIOL
(Biological study)
(Bag-1; apoptin in induction of p53-independent apoptosis in
transformed cells, use in **tumor** therapy, apoptin
localization, and diagnostic test for cell-transforming activity)

	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
1	BRS	L1	31	BAG near3 protein	USPAT	1999/12/21 16:11			0
2	BRS	L2	0	1 near30 (cancer or carcinoma or malignan\$4 or tumor or tumour or metastis\$4)	USPAT	1999/12/21 16:12			0
3	BRS	L3	12	1 and (cancer or carcinoma or malignan\$4 or tumor or tumour or metastis\$4)	USPAT	1999/12/21 16:13			0
4	BRS	L4	38	(bag near3 gene) or (bag-1n or bag-1m or bag-1l or bag-2 or bag-3 or bag-4 or bag-5)	USPAT	1999/12/21 16:14			0
5	BRS	L5	10	4 and (cancer or carcinoma or tumour or tumor or carcinoma or malignan\$4 or metastasis\$3)	USPAT	1999/12/21 16:15			0